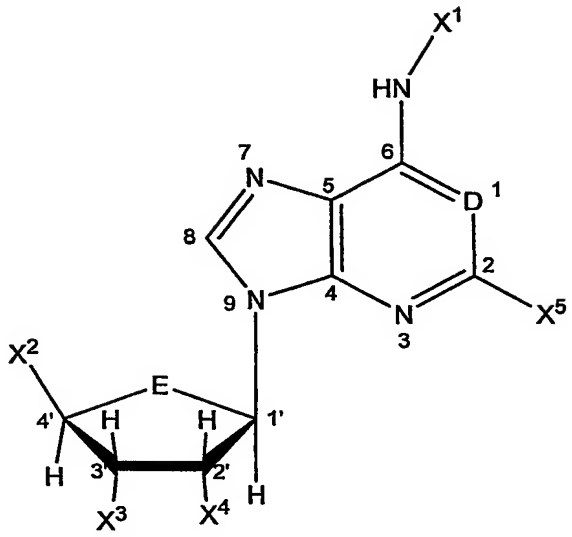
CLAIMS

1. A product which is a compound of the formula:



wherein

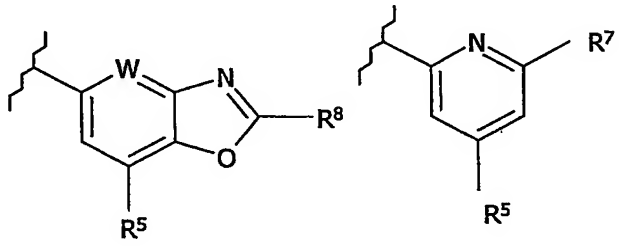
D is N or CH;

E is O, S or CH_2;

X^1 is a group of the formula $-CR^{20}R^{21}$-CYCLE, where

R^{20} and R^{21} are the same or different and H, F or CH_3;

CYCLE is of formula (II) or formula (III):



(II) (III)

where:

R^5 is iodine, bromine, methyl or trifluoromethyl;

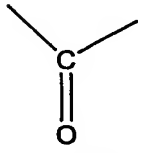
R^7 is H, halogen, C_1-C_{10} acyl, OR^{11}, CO_2R^{11} or $CONR^{11}$ where R^{11} is C_1-C_{10} hydrocarbyl optionally containing one or more in-chain and/or in-ring -O- linkages;

R^8 is $-NR^9R^{10}$ or $-COR^9$, where R^9 and R^{10} are each independently methyl or ethyl; and

W is N or CH;

.X^2 is hydroxymethyl, (C_1-C_3)alkoxymethyl, (C_3-C_5)cycloalkoxy methyl, carboxy, (C_1-C_3)alkoxycarbonyl, (C_3-C_5)cycloalkoxy-carbonyl, 1,1-aminoiminomethyl, 1,1-(mono-N- or di-N,N-(C_1-C_4)alkylamino)iminomethyl, 1,1-(mono-N- or di-N,N-(C_3-C_5)cycloalkylamino)iminomethyl, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylaminocarbonyl, mono-N- or di-N,N-(C_3-C_5)cycloalkyl-aminocarbonyl or N-(C_1-C_4)alkyl-N-(C_3-C_5)cycloalkylamino-carbonyl;

X^3 and X^4 are each independently hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, OR^a or NR^aR^b, where R^a and R^b are independently hydrogen, alkyl, aralkyl, carbamoyl, alkyl carbamoyl, dialkylcarbamoyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, or, when X^3 and X^4 are both OR^a, the two R^a groups together may form



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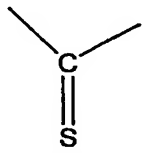

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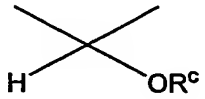
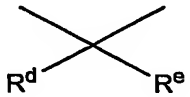


where R^c is hydrogen or alkyl,



where R^d and R^e are independently hydrogen, alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

X^5 is H, halogen, (C_1-C_{10})alkyl, fluorinated (C_1-C_{10}) alkyl (e.g. trifluoromethyl), (C_1-C_{10}) alkoxyalkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylether, (C_1-C_{10})thioalkoxy, (C_1-C_{10})alkylthio, amino, (C_1-C_{10})alkylamino, $-COX^6R^{25}$ where X^6 is O or NH and R^{25} is (C_1-C_4)alkyl optionally terminally substituted by an aryl or a heteroaryl group and additionally or alternatively terminally substituted by hydroxy, (C_2-C_{10})alkenyl, (C_2-C_{10})alkynyl, or is (C_2-C_{10})alkenyl, (C_2-C_{10})alkynyl in either case terminally substituted by an aryl or heteroaryl group and, when having a terminal methylic carbon atom, optionally further terminally substituted by hydroxy,

or a pharmaceutically acceptable salt or prodrug thereof or a pharmaceutically acceptable salt of such a prodrug.

2. A product of claim 1, wherein

D is N;

E is O;

X^2 is mono-N- or di-N,N(C_1-C_4)alkylaminocarbonyl, mono-N-

or di-, N-(C_3-C_5)cycloalkylaminocarbonyl or N-(C_1-C_4)alkyl-N- (C_3-C_5)cycloalkylaminocarbonyl;

X^3 is OH or NH_2;

X^4 is OH;

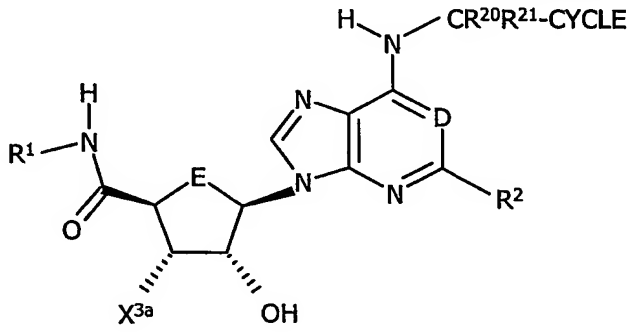
X^5 is H, halogen, (C_1-C_{10})alkyl, trifluoromethyl, (C_2-C_{10})alkenyl, (C_2-C_{10})alkynyl, or either of the latter two groups where terminally substituted as defined in claim 1.

3. A product of claim 1 or claim 2 wherein X^5 is halogen.

4. A product of claim 3 wherein X^5 is bromine or chlorine.

5. A product of any preceding claim wherein R^{20} and R^{21} are both H.

6. A product of claim 1 wherein the compound is of formula (V):



(V)

where:

-$CR^{20}R^{21}$-CYCLE, D and R^2 are as defined in claim 1;

E is O, S or CH_2 (e.g. E is O and optionally D is N and R^2 is Cl or other halogen);

R^1 is C_1-C_4 alkyl; and

X^{3a} is -OH or -NH_2.

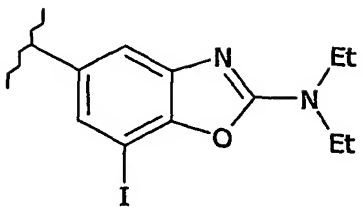
7. A product of claim 6 wherein E is O.

8. A product of any preceding claim wherein CYCLE is of formula (II).

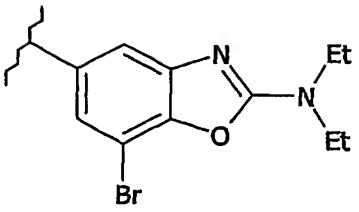
9. A product of claim 8 wherein W is N.

10. A product of claim 8 or claim 9 wherein R^8 is dimethylamino or diethylamino.

11. A product of claim 8 wherein CYCLE is selected from the group consisting of the following moieties:



(1)



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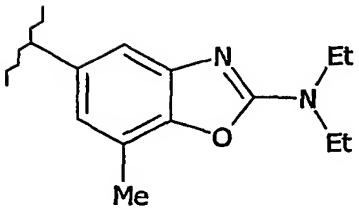

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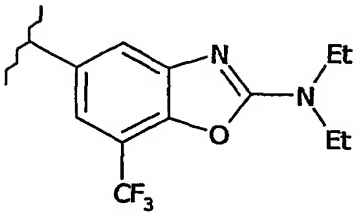

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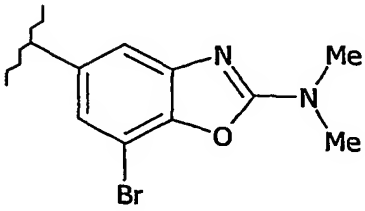

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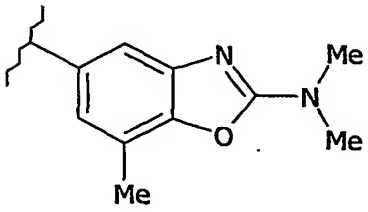

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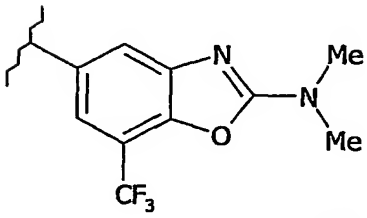

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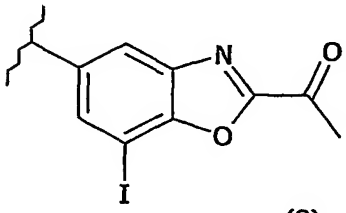

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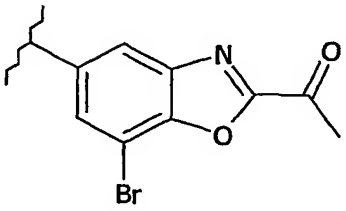

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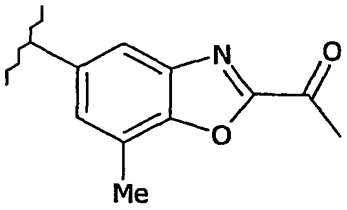

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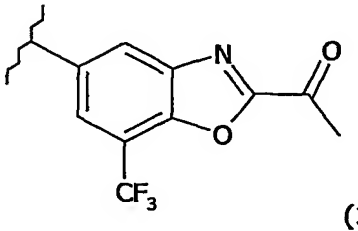

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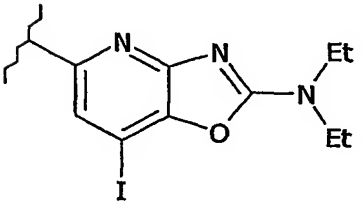

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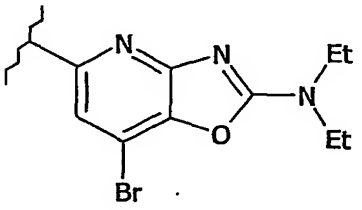

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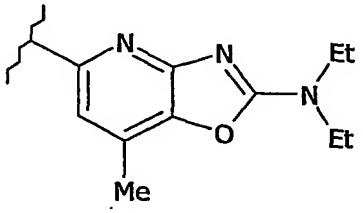

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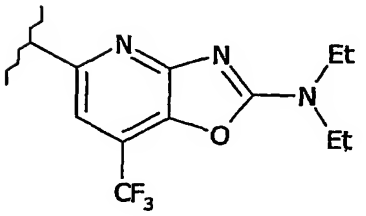

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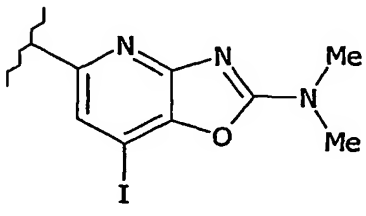

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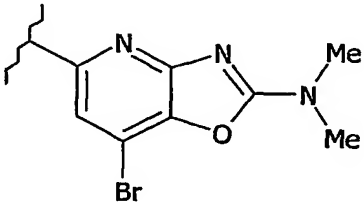

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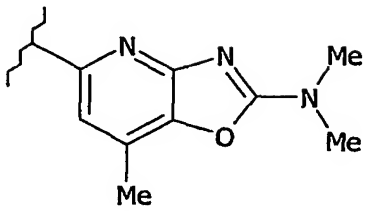

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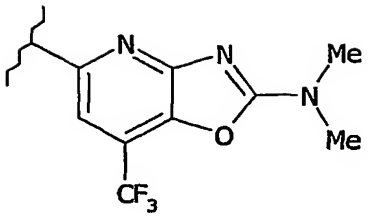

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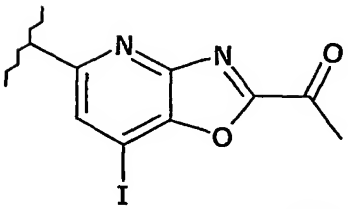

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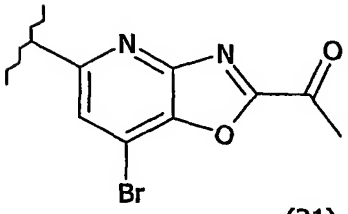

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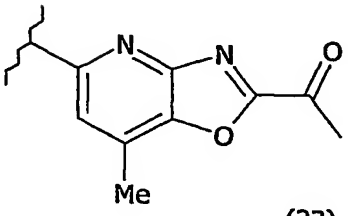

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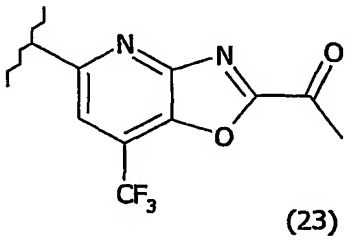
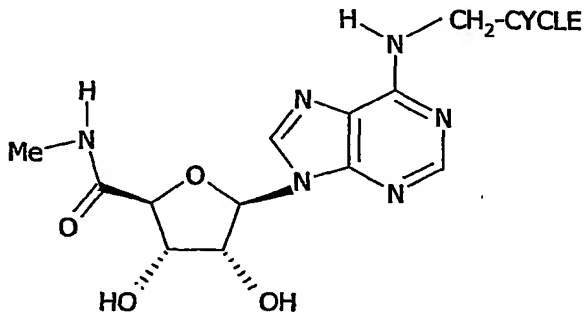


(23)

12. A product of claim 11 wherein CYCLE is of formula 1, 2, 3 or 4; or of formula 12, 13, 14 or 15.

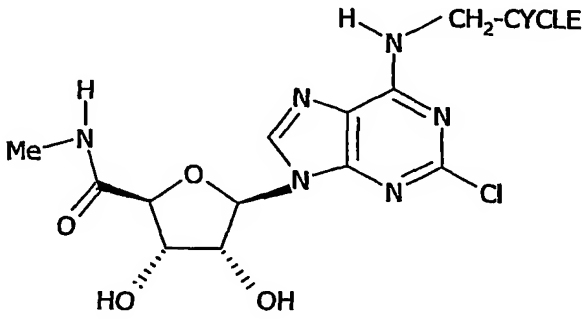
13. A product of any of claims 8, 11 and 12 wherein the compound is of formula (VI):



(VI)

where CYCLE is a group of formula (II).

14. A product of any of claims 8, 11 and 12 wherein the compound is of formula (VII):

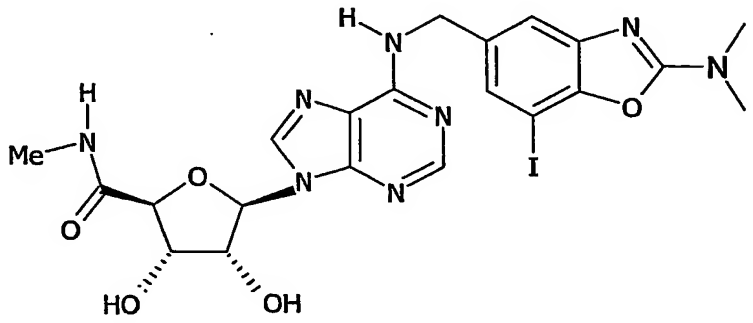


(VII)

where CYCLE is a group of formula (II).

15. A modification of a product of claim 13 or claim 14 in which the 3' -OH group is replaced by another X^3 or X^{3a} group.

16. A product of any preceding claim in which the compound is not

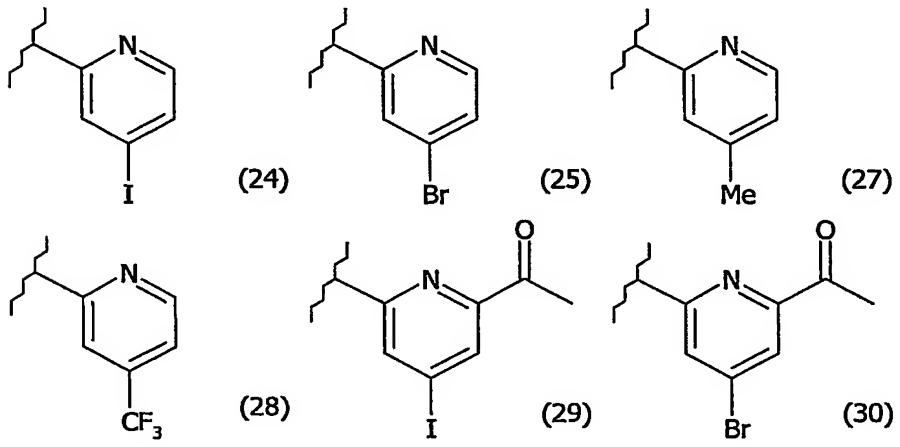


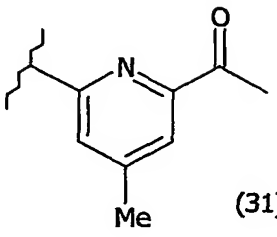
17. A product of any of claims 1 to 7 wherein CYCLE is of formula (III).

18. A product of claim 17 wherein R7 is C_1-C_{10} acyl wherein acyl is -COR^{12} in which R^{12} is hydrocarbyl or hydrocarbyl containing one or ore in-chain and/or in-ring -O- linkages.

19. A product of claim 17 wherein CYCLE is selected from the group consisting of the following moieties:

The invention therefore includes compounds having the following CYCLE moieties:

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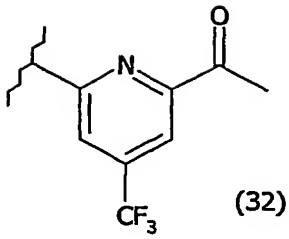
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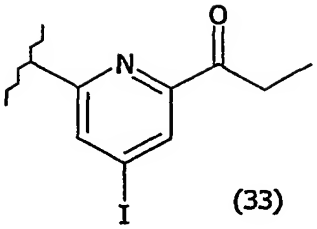
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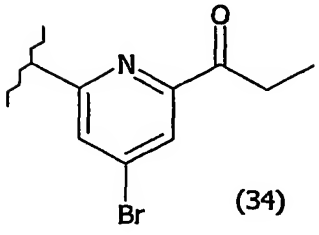
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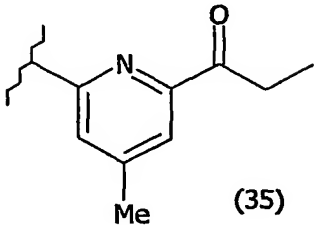
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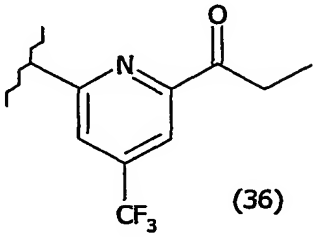
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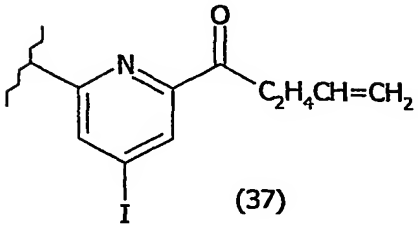
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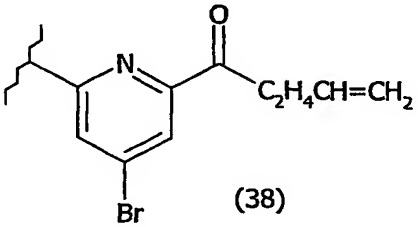
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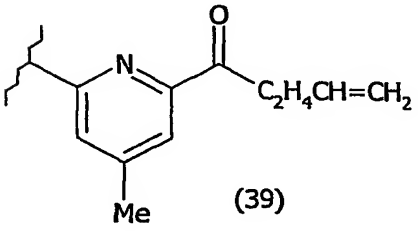
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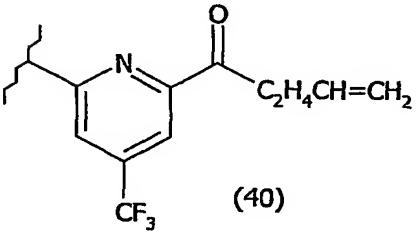
(40)

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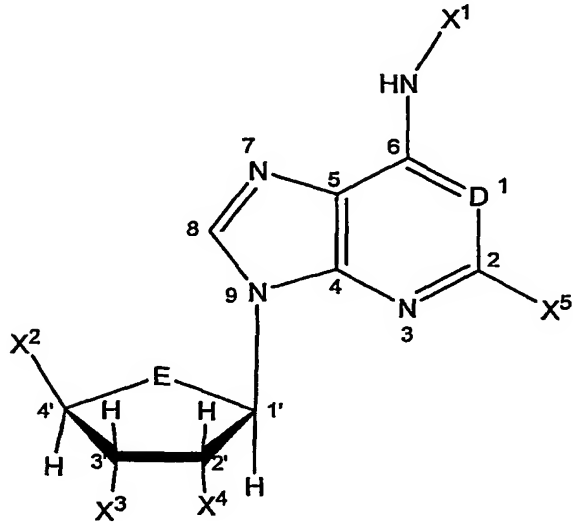
20. A compound of formula (VIII):

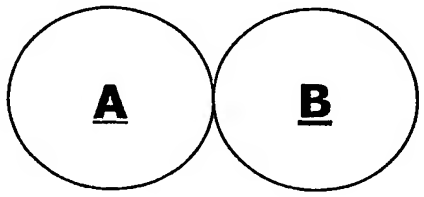

(VIII)

wherein

D is N or CH;

E is O, S or CH_2;

X^1 is of the formula $-CR^{20}R^{21}$-CYCLE where R^{20} and R^{21} are the same or different and H, F or CH_3; and CYCLE is a bicyclic (fused) heteroaromatic ring of the formula



wherein

ring A is a 5- or 6- membered ring characterised by the following features (in which ring positions are numbered relative to the linkage to $-CR^{20}R^{21}-$):

i. a carbon atom at the 1-position;

ii. carbon atom as CH or a nitrogen atom at position 2;

iii. it is 3, 4 fused to ring B;

iv. the 5-position ring atom is substituted by a moiety R^5 which is H, halogen, or an organic moiety having from 1 to 6 plurally valent atoms in addition to monovalent atoms selected from hydrogen and halogen;

v. if a 6-membered ring, it has at the 6-position a nitrogen, or –CM- where M is H, CH_3 or F;

ring B is a 5 or 6 membered ring characterised by the following features:

(a) an in-ring heteroatom including O, N or S joined to the 4-position of ring A;

(b) said in-ring heteroatom is joined within the ring secondly to a carbon which is substituted by a moiety R^8 which is $-N(C_2H_5)_2$;

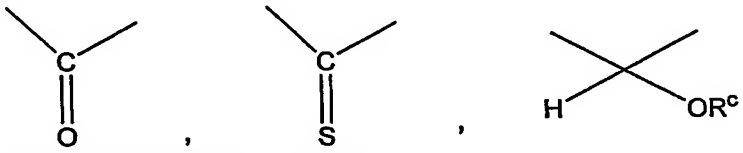
(c) an in-ring atom joined to the 3-position of ring A which is N,O, S or C, said C being in the form of a CH or CO group;

(d) in the case of a 6-membered ring, the remaining ring member is nitrogen or carbon in the form of CH;

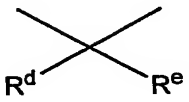
X^2 (the 4' substituent) is hydroxymethyl, (C_1-C_3)alkoxymethyl, (C_3-C_5)cycloalkoxy methyl, carboxy, (C_1-C_3)alkoxycarbonyl, (C_3-C_5)cycloalkoxycarbonyl, 1,1-aminoiminomethyl, 1,1-(mono-N- or di-N,N-(C_1-C_4)alkylamino)iminomethyl, 1,1-(mono-N- or di-N,N-(C_3-C_5)cycloalkyl-amino)iminomethyl, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylaminocarbonyl, mono-N- or di-N,N-(C_3-C_5)cycloalkylaminocarbonyl or N-(C_1-C_4)alkyl-N-(C_3-C_5)cycloalkylaminocarbonyl;

X^3 and X^4 are each independently hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, OR^a NR^aR^b, where R^a and R^b are independently hydrogen (most preferably X^3 and X^4 are OH), alkyl, aralkyl,

carbamoyl, alkyl carbamoyl, dialkylcarbamoyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, or, when X^3 and X^4 are both OR^a, the two R^a groups together may form



where R^c is hydrogen or alkyl,



where R^d and R^e are independently hydrogen, alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

X^5 is H, halogen, $(C_1\text{-}C_{10})$alkyl, fluorinated $(C_1\text{-}C_{10})$ alkyl (e.g. trifluoromethyl), $(C_1\text{-}C_{10})$ alkoxyalkyl, $(C_1\text{-}C_{10})$alkoxy, $(C_1\text{-}C_{10})$alkylether, $(C_1\text{-}C_{10})$thioalkoxy, $(C_1\text{-}C_{10})$alkylthio, amino, $(C_1\text{-}C_{10})$alkylamino, $-COX^6R^{25}$ where X^6 is O or NH and R^{25} is $(C_1\text{-}C_4)$alkyl optionally terminally substituted by an aryl or a heteroaryl group [for example phenyl or a 5- or 6-membered heteroaryl group] and additionally or alternatively terminally substituted by hydroxy, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, or is $(C_2\text{-}C_{10})$alkenyl or $(C_2\text{-}C_{10})$alkynyl in either case terminally substituted by an aryl or heteroaryl group [for example phenyl or a 5- or 6-membered heteroaryl group] and, when having a terminal methylic carbon atom, optionally further terminally substituted by hydroxy.

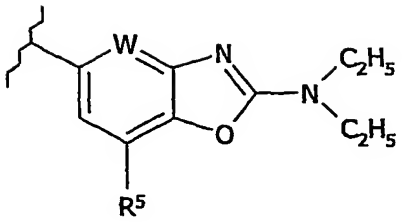
21. A compound of claim 20 wherein R^5 has from 1 to 4 plurally valent atoms.

22. A compound of claim 21 wherein the plurally valent atoms are selected from carbon, oxygen, sulfur and nitrogen.

23. A compound of claim 22 wherein R^5 is CH_3, CF_3, OH or NH_2.

24. A compound of claim 20 wherein R^5 is H, I, Br or Cl.

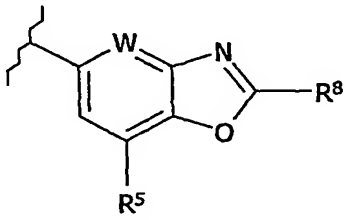
25. A compound of any of claims 20 to 24 wherein CYCLE is of formula (IX)



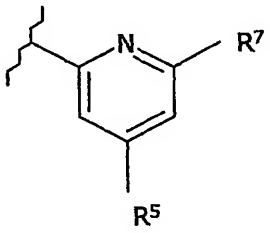
(IX)

26. A compound of any of claims 20 to 25 wherein where R^{20} and R^{21} are both hydrogen.

27. An adenosine analogue-type A3 receptor agonist having an N6 nitrogen substituted by a group of the formula $-CR^{20}R^{21}$-CYCLE where R^{20} and R^{21} are the same or different and H, F or CH_3; and CYCLE is of formula (II) or formula (III):



(II)



(III)

where:

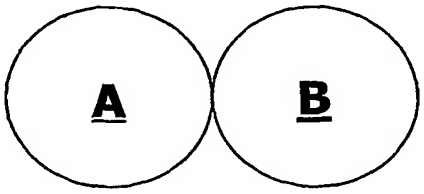
R^5 is iodine, bromine, methyl or trifluoromethyl;

R^7 is H, halogen, C_1-C_{10} acyl, OR^{11}, CO_2R^{11} or $CONR^{11}$ where R^{11} is C_1-C_{10} hydrocarbyl optionally containing one or more in-chain and/or in-ring -O- linkages;

R^8 is $-NR^9R^{10}$ or $-COR^9$, where R^9 and R^{10} are each independently methyl or ethyl; and

W is N or CH.

28. An adenosine analogue-type A3 receptor agonist having an N6 nitrogen substituted by a group of the formula $-CR^{20}R^{21}$-CYCLE where R^{20} and R^{21} are the same or different and H, F or CH_3; and CYCLE is a bicyclic (fused) heteroaromatic ring of the formula



wherein

ring A is a 5- or 6- membered ring characterised by the following features (in which ring positions are numbered relative to the linkage to $-CR^{20}R^{21}$-):

i. a carbon atom at the 1-position;

ii. carbon atom as CH or a nitrogen atom at position 2;

iii. it is 3, 4 fused to ring B;

iv. the 5-position ring atom is substituted by a moiety R^5 which is H, halogen or an organic moiety having from 1 to 6 plurally valent atoms in addition to monovalent atoms selected from hydrogen and halogen;

v. if a 6-membered ring, it has at the 6-position a nitrogen, or –CM- where M is H, CH_3 or F;

ring B is a 5 or 6 membered ring characterised by the following features:

(a) an in-ring heteroatom including O, N or S joined to the 4-position of ring A;

(b) said in-ring heteroatom is joined within the ring secondly to a carbon which is substituted by a moiety R^8 which is $-N(C_2H_5)_2$;

(c) an in-ring atom joined to the 3-position of ring A which is N,O, S or C, said C being in the form of a CH or CO group;

(d) in the case of a 6-membered ring, the remaining ring member is nitrogen or carbon in the form of CH.

29. A product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28 for use as a medicament.

30. A product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28 for use in a method for selectively activating A_3 adenosine receptors in a mammal.

31. The use of a product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28 for the manufacture of a medicament for use in a method for selectively activating A_3 adenosine receptors in a mammal.

32. The use of a product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28 for the manufacture of a medicament for use for the reduction of tissue damage resulting from ischaemia or hypoxia.

33. The use of a product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28 for the manufacture of a medicament for use for preconditioning the heart to protect it from ischaemic damage.

34. The use of any of claims 31 to 33 wherein the medicament is for intravenous administration.

35. The use of any of claims 31 to 34 wherein the medicament is for use in combination therapy with another cardiovacular drug.

36. A pharmaceutical composition comprising a product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28.

37. A pharmaceutical composition of claim 36 which is an intravenous formulation.

38. The use in a medicament of an N6 substituent as defined in claim 27 or claim 28 to increase the A_3 receptor specificity of an adenosine analogue of which the remainder is compatible with the adenosine A_3 receptor for agonist use.

39. A method of stimulating adenosine A_3 receptors, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a product of any one of claims 1 to 26 or an agonist of claim 27 or claim 28.

40. A method of reducing tissue or organ damage (e.g., substantially preventing tissue or organ damage, inducing tissue or organ protection) resulting from ischaemia or hypoxia, comprising administering to a mammal in need of such treatment a therapeutically effective amount of an agent selected from a product of any one of claims 1 to 26 and agonist of claim 27 or claim 28.